

Chemerin as a New Marker in Iraqi Newly Diagnosed Type 2 Diabetes Mellitus

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Abstract:

Chemerin is a novel adipokine, suggested to be involved in insulin resistance in obesity and type 2 diabetes and may be an attractive candidate for assessing risk of atherosclerotic cardiovascular disease.

The aim of this study was to examine the role of chemerin as a new marker in newly diagnosed type 2 diabetes mellitus accompanied with obesity and study the effect of age and gender in chemerin concentration.

This study included 53 (24 male and 29 female) newly diagnosed type 2 diabetic patients who visited the National Diabetic Center, University of AL-Mustansiriyah. Those cases were referred to the Center during the period from November 2013 until the end of August 2014. They were subdivided according to body mass index; their age range was (38-52), and (35) healthy subjects were selected as a control group; they were well matched age with patients group.

There was a significant increase in waist, waist/hip ratio, body mass index, fasting blood sugar, glycated hemoglobin, total cholesterol, triglycerides, low density lipoprotein cholesterol, C-peptide, homeostasis model assessment for insulin resistance 2, and chemerin levels in newly diagnosed diabetic patients as compared to the control, (P=0.0001).

The results appear there was a significant decrease in high density lipoprotein cholesterol. A significant difference was found in serum chemerin levels among lean, overweight, and obese of newly diagnosed type 2 diabetic patients, (P=0.01). There was a significant positive correlation between serum chemerin versus fasting blood sugar, glycated hemoglobin, lipid profile except high density lipoprotein cholesterol, C-peptide, and homeostasis model assessment for insulin resistance 2, while there was a significant negative correlation between high density lipoprotein cholesterol and chemerin, (P<0.05).

It can be concluded that high levels of serum chemerin found in newly diagnosed type 2 diabetic patients suggest that chemerin may play an important role in the pathogenesis of insulin resistance and type 2 diabetes mellitus.

Key Words: Chemerin, type 2 diabetes mellitus, obesity, insulin resistance.

الكيميرين كدلالة جديدة لدى المرضى العراقيين المصابين بداء السكري النوع الثاني المشخصين حديثاً

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الكيميرين هو أديبوكاين حديث، وأقترح أن يتضمن في مقاومة الانسولين في السمنة ومرض السكري من النوع الثاني وربما يستعمل لتقييم مخاطر الإصابة بأمراض تصلب الشرايين القلب والأوعية الدموية. الهدف من هذا البحث هو دراسة دور الكيميرين كدلالة جديدة لدى مرضى السكري من النوع الثاني المشخصين حديثاً والذين يعانون من البدانة ودراسة تأثير العمر والجنس على تركيز الكيميرين. تضمنت هذه الدراسة 53 شخصاً (24 ذكور و 29 أنثى) من المصابين حديثاً بالنوع الثاني من مرض السكري الذين راجعوا المركز الوطني للسكري/ الجامعة المستنصرية خلال الفترة من تشرين الثاني 2013 حتى نهاية اب 2014،

وقد تم تقسيمهم وفقاً لمؤشر كتلة الجسم، وكان معدل أعمارهم بين (38-52) سنة، وقد تم اختيار (35) شخصاً سليماً كمجموعة سيطرة وتم ضبط العمر مع مجموعته المرضية.

أظهرت النتائج أن هناك زيادة معنوية في محيط الخصر، محيط الخصر/الورك، مؤشر كتلة الجسم، الكيميرين، السكر في الدم، الهيموكلوبين السكري، الدهون الكلية، الدهون ثلاثية الكليسيرايد، البروتين الدهني قليل الكثافة، الببتيد-C، مقاومة الأنسولين حسب طريقة (HOMA 2)، والكيميرين لدى مرضى السكري من النوع الثاني والمشخصين حديثاً بالمقارنة مع السيطرة، (P= 0.0001). أيضاً، كانت هناك اختلافات معنوية في مستويات الكيميرين في المصل بين الأشخاص النحيفين، البدناء، والذين يعانون من السمنة المفرطة، (P= 0.01). كانت هناك علاقة إيجابية ذات دلالة إحصائية بين الكيميرين في المصل مقابل السكر في الدم، الهيموغلوبين السكري، ومستوى الدهون في الدم باستثناء البروتين الدهني عالي الكثافة، الببتيد-C، ومقاومة الأنسولين حسب طريقة (HOMA 2) بينما كانت هنالك علاقة سلبية معنوية بين البروتين الدهني عالي الكثافة والكيميرين، (P<0.05).

يمكن الاستنتاج أن ارتفاع مستويات الكيميرين التي وجدت في مصل مرضى السكري من النوع الثاني والمشخصين حديثاً ممكن أن تلعب دوراً هاماً في تطور مقاومة الأنسولين ومرض السكري من النوع الثاني.

مفتاحية: الكيميرين، مرض السكري من النوع الثاني، السمنة، مقاومة الأنسولين.

Introduction:

Diabetes mellitus (DM) is one of the most common chronic diseases in nearly all countries, and continues to increase in numbers and significance, as altering lifestyles lead to reduced physical activity, and increased obesity^[1].

The impairment of glucose metabolism has been connected with a complex group of risk factors that contribute to increase insulin resistance (IR) with aging. Obesity, and falling levels of physical activity are vital contributors to the rise of DM worldwide^[2].

Dysregulation of pro inflammatory and anti inflammatory adipokines secretion in obesity may supply as a pathogenic link between obesity, IR and cardiovascular diseases^[3].

Chemerin is a dipokine recognized recently, which may participates in the regulation of adipocyte formation and differentiation as well as the regulation of insulin signaling pathway, and may play an important role in IR and glycolmetabolism^[4]. Serum chemerin concentrations are elevated in obese, IR, and inflammatory states *in vivo* and suggested to be an obvious cause of IR^[5].

Several groups have recently, reported that chemerin is an adipokine that enhances insulin-dependent glucose uptake in adipocytes *in vitro*, suggesting the involvement of chemerin in glucose homeostasis^[6].

Chemerin peptides are short peptides (on the order of 9 amino acids) that are produced from the carboxyl terminal of the chemokine chemerin. A particular synthetic chemerin-derived peptide, termed C15 which was found to promote phagocytosis and efferocytosis in peritoneal macrophages at picomolar concentrations. C15 enhanced macrophage clearance of microbial particles and apoptotic cells^[7].

Chemerin is an agonist of the orphan G-protein coupled receptor chemokine-like receptor 1 (CMKLR1, ChemR23)^[8]. Chemerin and its receptor/ ChemR23 are expressed abundantly in adipose tissue, suggesting its function in autocrine/ paracrine fashion^[9]. Recently, chemerin is a retinoic acid receptor responder 2, tazarotene- induced gene 2. It is secreted as an 18 kDa inactive pro-protein and undergoes extracellular serine protease cleavage of the C-terminal portion of the protein to generate the 16 kDa active chemerin which is present in plasma and serum, and N-terminal cleavage before it is secreted as an inactive precursor protein, pro-chemerin^[10]. These findings showed that chemerin has multiple cleavage sites in the C-terminal domain. In order to reach its maximal anti-inflammatory effects, bioactivity of chemerin is dependently regulated by proteolytic cleavage in the C-terminal region^[11].

It may connect obesity and inflammation since chemerin is a proinflam-

matory cytokine that recruits and activates immune cells and contributes to inflammation by promoting macrophage adhesion to vascular cell adhesion molecule-1 (VCAM-1) and fibronectin^[12].

The present study aimed to investigate the role of chemerin as a new marker in the pathogenesis of newly diagnosed type 2 DM accompanied with obesity depending on body mass index and study the effect of age and gender in chemerin concentration.

Materials and Methods:

This study included 53 (24 male and 29 female) newly diagnosed type 2 diabetic patients who visited the National Diabetic Center, AL- Mustansiriyah University. Those cases were referred to the Center during the period from November 2013 until the end of August 2014. They were subdivided according to BMI into 22 lean (BMI < 25 kg/m²), 17 overweight (BMI 25-29 kg/m²), and 14 obese (BMI ≥ 30 kg/m²). Their age range was (38-52) years. Complete clinical examination was done for all patients to exclude any diabetic complications such as neurologic, cardiac, kidney and eye complications, and (35) healthy subjects were selected as a control group; they were well matched age with patients group. A sample of 10 milliliters venous blood was collected from each subject after an overnight fasting.

Measurements:

Weight and height were measured for each subject then the body mass index (BMI) was calculated by dividing weight (kg) by height (in meters). Waist and hip was measured for every patients and control according to world health organization (WHO) protocol^[13].

The serum samples were used to estimate the following parameters:

Glucose was determined, by using the enzymatic colorimetric method^[14]. The Bio-Rad VARIANT hemoglobin A1C program utilizes principles of ion-exchange high-performance liquid chroma-

Date of acceptance: 15-12-2014

tography for the automatic and accurate separation of glycated hemoglobin (HbA1c)^[15].

C-Peptide was determined by immune-radiometric assay (IRMA) method^[16].

Homeostasis model assessment for insulin resistance 2 (HOMA2-IR) was calculated using HOMA 2 calculator software downloaded freely.

Total cholesterol (TC), triacylglycerol (TAG), and high density lipoprotein cholesterol (HDL-C) were determined by enzymatic colorimetric method^[17,18,19].

Low density lipoprotein cholesterol was estimated by the equation of Friedewald *et al.*^[20].

Chemerin was determined by a solid phase enzyme linked immunosorbent assay (ELISA) method using (CUSABIO kit-CSP-E10398h)^[21].

Statistical Analysis:

Statistical package of social science (SPSS) version 9.0 was used. Data was summarized as mean ± SD. T test was used for analysis of data. Statistical significance was set at P<0.05.

Results:

Characteristics of newly diagnosed DM group and the control group were summarized in table-1. There was a significant increase in waist, waist/hip (W/H) ratio, FBS, HbA1c, TC, TAG, LDL-C, VLDL, C-peptide, HOMA 2-IR, and chemerin in newly diagnosed DM group as compared to the control group, while there was a significant decrease in HDL-C in chemerin in newly diagnosed DM as compared to the control group.

Table-2 showed the effect of BMI on chemerin levels in newly diagnosed DM group. There was a significant increase in serum chemerin in newly diagnosed DM patients who were obese as compared to lean and overweight groups, (P=0.01).

Table-3 showed a significant positive correlation between serum

chemerin versus W/H ratio, FBS, HbA1c, TC, TAG, LDL-C, VLDL, C-peptide, and HOMA2-IR in newly diagnosed DM group, while a negative correlation was found between chemerin and HDL-C in newly diagnosed DM group.

Figure-1 demonstrated distribution of chemerin concentration according to age in newly diagnosed DM patients.

Figure-2 explained comparison of chemerin concentration between male and female in newly diagnosed DM patients.

Table-1: Characteristics of newly diagnosed diabetes mellitus group and the control group.

Parameter	Newly Diagnosed DM (n=53)	Control (n=35)	P Value
Waist (Cm)	92.35 ± 1.52	74.80 ± 1.38	0.0001***
Hip (Cm)	103.66 ± 1.29	103.02 ± 1.55	0.756 NS
W/H ratio	0.89 ± 0.01	0.73 ± 0.01	0.0001***
BMI (Kg/m ²)	27.07 ± 3.44	25.98 ± 3.44	0.50 NS
FBS (mg/dl)	135.01 ± 6.93	90.48 ± 6.93	0.0001***
HbA1c (%)	7.99 ± 0.18	4.84 ± 0.05	0.0001***
TC (mg/dl)	189.83 ± 5.56	150.22 ± 1.93	0.0001***
TAG (mg/dl)	154.13 ± 11.77	105.28 ± 3.18	0.0001***
HDL-C (mg/dl)	47.13 ± 1.27	57.68 ± 0.94	0.0001***
LDL-C (mg/dl)	111.28 ± 4.69	71.91 ± 2.03	0.0001***
VLDL (mg/dl)	31.41 ± 2.49	20.62 ± 0.61	0.0001***
C-Peptide (ng/ml)	3.57 ± 0.14	1.82 ± 0.05	0.0001***
HOMA 2-IR	3.60 ± 0.18	1.39 ± 0.04	0.0001***
Chemerin (µg/l)	125.91 ± 9.8	65.66 ± 1.12	0.0001***

NS: not significant

Table-2: Effect of BMI in chemerin in newly diagnosed diabetes mellitus group.

	BMI (Mean ± SD)			P Value
	Lean (n=22)	Overweight (n=17)	Obese (n=14)	
Chemerin (µg/l)	67.35 ± 3.00	91.00 ± 10.57	225.00 ± 24.92	0.01**

Table-3: The correlations between serum chemerin and other parameters in newly diagnosed diabetes mellitus group.

Chemerin	Correlation coefficient (r)	Chemerin	Correlation coefficient (r)
W/H ratio	0.380*	HDL-C	-0.389*
FBS	0.292*	LDL-C	0.296*
HbA1C	0.482*	VLDL	0.530*
TC	0.465*	C-Peptide	0.472*
TAG	0.530*	HOMA 2-IR	0.390*

*P<0.05

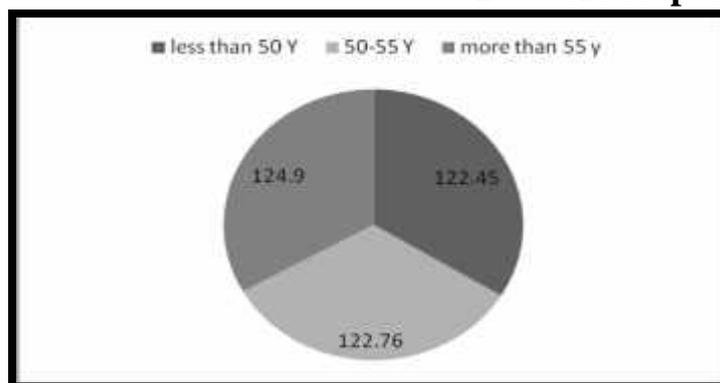


Figure-1: Distribution of chemerin concentration according to age in newly diagnosed diabetes mellitus group.

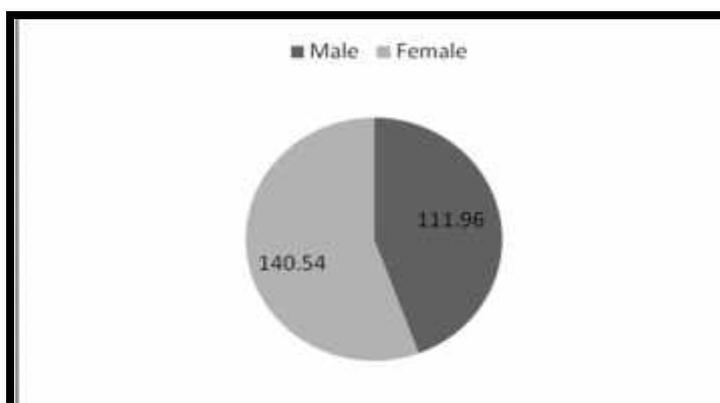


Figure-2: Comparison of chemerin concentration between male and female in newly diagnosed diabetes mellitus group.

Discussion:

Diabetes is an essential health problem since the incidence of it is continuously increasing. Early diagnosis is important as type 2 diabetes begins long before it is diagnosed, leading to a complicated course of the disease, in order to avoid delay in the diagnosis of type 2 diabetes, new predictors and pathways for type 2 diabetes are mounting. Adipocytokines such as chemerin may play important roles in the pathogenesis of DM and IR [22].

However, the relationship between chemerin levels and IR remains controversial, whether the high levels of chemerin is the outcome of IR or an attributed factor for IR. It has shown that hyperinsulinemia associated with IR could up-regulate chemerin expression in adipose tissue [23].

Obesity-associated disorders including metabolic syndrome, diabetes,

atherosclerosis, hypertension, and coronary artery disease are associated with dysregulated adipokines expression [24].

The results of the present study revealed that the waist, waist/hip ratio, FBS, TC, TAG, LDL-C, C-peptide, HOMA 2-IR, and serum chemerin levels were significantly higher in newly diagnosed type 2 DM patients when compared to the control group, which is in agreement with the previous study [25].

Serum chemerin concentrations are elevated in obese, insulin-resistant, and inflammatory states *in vivo* and recommended to be an evident cause of IR in obesity [26].

There was a significant difference in chemerin concentrations according to BMI among lean, overweight, and obese patients. However, studies including the current investigation, have consistently reported that the serum chemerin levels are positively interconnected with BMI,

suggesting that the amount of adipose tissue is a main regulator of the serum chemerin levels. Morbidly obese patients were integrated in the earlier studies, particularly in the type 2 DM groups, and the findings suggest that this condition might pretense the effect of type 2 DM on chemerin because of the strong effect of obesity on serum chemerin levels [27, 28].

A recent study by Johanna *et al.* in 2010 reported that chemerin levels associated with BMI and waist-to-hip ratio [29].

In the present data, serum chemerin correlated positively with each of FBS, HbA1c, TC, TAG, LDL-C, C-peptide, and HOMA 2-IR in newly diagnosed type 2 DM patients. While, there was a significant negative correlation between chemerin and HDL-C. These findings are in agreement with many reports [30,31, 32]. Homeostasis model assessment for insulin resistance 2 remained positively associated with chemerin levels. Thus, the present results can confidently conclude that chemerin levels may influence glucose homeostasis and therefore may lead to the development of IR [33]. It is potential that in obesity, elevated levels of chemerin predominantly induce IR in muscle and even if chemerin stimulates β -cell function and suppresses gluconeogenesis in the liver, the net glucose tolerance may be deteriorated. It has been reported that serum chemerin levels were associated with IR in mice and humans, which supports this hypothesis [34].

As referred, aging is known to be connected with increasing IR, weight, and adiposity gain. According to present data, aging in newly diagnosed DM patients is associated with an altered adipokine secretion, as shown by the means differences, figure-1. Bozaoglu *et al.* [35] found that chemerin levels increased with age and that there appears to be no diurnal variation in chemerin levels.

The present results showed that there was a significant difference in chemerin concentrations between male and female in newly diagnosed type 2 DM

Date of acceptance: 15-12-2014

patients, figure (2). Lehrk *et al.* [36] found that serum chemerin levels in female were elevated more than in male, which is in agreement with the results of this study; these differences may be due to the differences in hormonal changes.

Conclusions:

Significant associations between serum chemerin levels and various parameters of the IR were observed in newly diagnosed type 2 DM. These findings suggest that chemerin may provide an interesting screening or diagnostic tool for DM, obesity and its complications in humans.

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